HED DOC. NO. 014549

DATE: April 23, 2001

MEMORANDUM

SUBJECT: ***OXYFLUORFEN*** - Report of the Hazard Identification Assessment Review Committee.

FROM: Kit Farwell, D.V.M.
Reregistration Branch 1
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair
and
Elizabeth Doyle, Ph.D., Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Felecia Fort, Risk Assessor
Reregistration Branch 1
Health Effects Division (7509C)

PC Code: 111601

On March 15, 2001, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for oxyfluorfen with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to oxyfluorfen was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions drawn at this meeting are presented in this report.

Committee Members in Attendance

Members present were: Bill Burnam, Beth Doyle, Pamela Hurley, Elizabeth Mendez, David Nixon, Jess Rowland, Yung Yang, Jonathan Chen, Ayaad Assaad, Brenda Tarplee (Exec. Sec.)

Member(s) in absentia: Paula Deschamp

Data evaluation prepared by: Kit Farwell, D.V.M., Toxicologist, RRB1

Also in attendance were: Whang Phang, Michael Metzger, Timothy Dole, Felecia Fort, Bob Zendzian, Bill Dykstra, Norman Birchfield, EFED

Data Evaluation / Report Presentation

____
Kit Farwell, D.V.M.
Toxicologist

1. INTRODUCTION

On March 15, 2001, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for oxyfluorfen with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to oxyfluorfen was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996.

Oxyfluorfen is a diphenyl ether herbicide structurally related to lactofen and acifluorfen. The diphenyl ether herbicides act by inhibiting protoporphyrinogen oxidase, which is the second-to-last enzyme in chlorophyll biosynthesis. This enzyme is the second-to-last enzyme in heme synthesis, as well (Birchfield and Casida, *Pesticide Biochemistry and Physiology*, 1997).

The older toxicity studies with oxyfluorfen used technical material of either 71% or 85% purity. The newer toxicity studies used a technical material of approximately 98% purity, which is the basis for the current registrations of oxyfluorfen. The newer technical material has similar impurities to the older technical material, but in reduced concentrations.

When there were studies with both the new and old technical material, consideration to an endpoint was given to the newer, 98% technical material which is the basis of the current registrations. All studies had doses adjusted for per cent a.i. and/or for analytical concentrations determined in the diet.

2. HAZARD IDENTIFICATION

2.1 Acute Reference Dose (RfD)

Study Selected: None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not Applicable

Uncertainty Factor(s): Not Applicable

Comments about Study/Endpoint/Uncertainty Factor: No appropriate endpoint was identified. Developmental toxicity in the 1997 developmental toxicity study in rabbits (MRID 44933102) using the 98% technical oxyfluorfen which is currently registered was considered for this endpoint. The developmental NOAEL in this study was based on increased late resorptions and resulting decreased number of live fetuses/doe in the high-dose group. This endpoint was not considered appropriate for use in risk assessment because the late resorptions were primarily due to late resorptions in one doe and were not statistically significant. The 1981 developmental toxicity study in rabbits (MRID 00094052) was not considered suitable as an endpoint because it used a 26.9% wettable powder formulation which was manufactured from the 71% a.i. technical material which is no longer manufactured.

Acute RfD: Not established

2.2 Chronic Reference Dose (RfD)

Study Selected: Chronic toxicity study in dogs. 870.4100 (83-1)

MRID No.: 00078767
and
Study Selected: Carcinogenicity study in mice 870.4200 (83-2a)

MRID No.: 00037939

Executive Summary for Chronic Toxicity Study in Dogs: In a chronic oral toxicity study (MRID 00078767 and 92136062), oxyfluorfen (71.4-73.8% a.i.) was administered to six beagle dogs/sex/dose in the feed (400 gm/day) at concentrations of 100, 600, or 3600-2000 ppm (3600 ppm for days 1-8, 0 ppm for days 9-14, 2800 ppm for days 15-28, and 2000 ppm from day 29 to termination) for up to 104 weeks. The equivalent average daily doses were 3.1, 18.5, or 61.0 mg/kg/day (males) and 3.0, 18.8, or 60.3 mg/kg/day (females) when corrected for purity and analytical concentration. Ten dogs/sex served as untreated controls. One mid-dose female was found dead during week 35 of unknown causes. A high-dose male was sacrificed moribund during week 83 due to inguinal herniation of the abdominal viscera. Treatment-related clinical signs included thin appearance and heavy lacrimation primarily at the high dose. Heavy lacrimation was noted in 6/8 high-dose dogs. Corresponding to this finding was epiphora in 1/4 males and 3/4 females at the high dose during ophthalmoscopic examination. In the first week of the study, the high dose animals had significant loss of body weight caused by lack of food consumption. As a consequence, the high dose was gradually lowered over 28 days from 3600 to 2000 ppm. At week 4, mean body weights for the high-dose males and females were 79-81% (n.s.) of controls and remained lower to study termination (70-75% of controls at week 104; n.s.). Overall weight gains at week 104 corresponded to 106%, 74%, and 11% of controls (males) and 61%, 44%, and 15% of controls (females) at the low, mid, and high doses, respectively. Food consumption was decreased in the high-dose group. There were decreases in hematocrit, hemoglobin, and erythrocyte values in high-dose males (values were 74-77% of controls) at week 104; decreased ($p<0.05$) hemoglobin values in high-dose males at weeks 13, 52, and 82 (84-89% of controls). Serum alkaline phosphatase activity was increased in high-dose males and females (225-884% of control values) and in mid-dose males (298% of control values) at termination, as well as during the study. No treatment-related gross lesions were observed at the interim or terminal sacrifices. Increased liver weights, generally dose-related, were seen at the interim and terminal sacrifices. Respective liver weights for low-, mid-, and high-dose males were 110, 147, and 147% of controls (absolute); 109, 153, and 195% of controls (relative); and for females, 106, 118, and 150% of controls (absolute) and 121, 144, and 222% of controls (relative) at termination. The only treatment-related histopathological lesion in the liver was slight to moderate bile pigmented hepatocytes in both sexes after 104 weeks (n.s.) and hepatocellular vacuolization was seen in high-dose females. The **LOAEL** is 600 ppm (males: 18.5 mg/kg/day; females: 18.8 mg/kg/day) based on decreased weight gains, increased alkaline phosphatase activity, increased absolute/relative liver weights. The **NOAEL** is 100 ppm (males: 3.1 mg/kg/day; females: 3.0 mg/kg/day). This study is classified **acceptable/guideline** and satisfies the guideline requirement for a chronic oral toxicity study (83-1b) in the dog.

<u>Executive Summary for Carcinogenicity Study in Mice:</u> In an oncogenicity study (MRID 00037939, 92136017), oxyfluorfen (RH-2915 Technical, 87.5% a.i.) was administered in the diet to 60 male and 60 female Charles River CD-1 mice at concentrations of 0 (negative control), 0 (ethanol control), 2, 20, and 200 ppm for up to 87 weeks. The corresponding dose levels (adjusted for % a.i.) were 0, 0, 0.3, 3.0, and 33.0 mg/kg/day for males, and 0, 0, 0.4, 4.0, and 42.0 mg/kg/day for females. One control group received only the basal diet; the second control group received the basal diet mixed with ethanol. There was an interim sacrifice of 5 mice/sex for both control groups and the high dose group. Body weights, body weight gain, and food consumption were similar in all groups. Liver toxicity was shown by increased liver weights, elevated enzyme levels, microscopic liver lesions, and liver tumors. Treatment-related toxicity was more pronounced in males. Absolute and relative liver weights were increased 23-35%, relative to controls, in high-dose animals. Microscopic lesions increased in livers of high-dose animals included hepatocyte necrosis, hepatic regeneration and hyperplastic nodules. Alkaline phosphatase (+110%) and SGPT (+77%) were increased in high-dose males. Combined hepatocellular adenomas and carcinomas were increased in 200 ppm males (8/52 vs 1/47 and 0/47 in the 2 control groups). This study was used to determine the Q1* for oxyfluorfen. The **LOAEL** is 200 ppm in male (33.0 mg/kg/day) and female (42.0 mg/kg/day) mice, based on liver toxicity (microscopic liver lesions; increased absolute and relative liver weights; and elevated liver enzymes. The **NOAEL** is 20 ppm for males (3.0 mg/kg/day) and females (4.0 mg/kg/day). This oncogenicity study in the mouse is classified **acceptable** for assessing the carcinogenic potential of oxyfluorfen.

<u>Dose and Endpoint for Establishing Chronic RfD:</u> NOAEL = 3.0 mg/kg/day based upon liver toxicity occurring in mice and dogs.

<u>Uncertainty Factor(s):</u> 100x to account for differences in inter- and intraspecies sensitivity

Comments about Study/Endpoint/Uncertainty Factor: This endpoint is appropriate for the route and duration of exposure. The same effects (liver toxicity) occurred in mice and dogs at comparable doses. The HIARC discussed results of the 90-day toxicity study in rats (98% a.i.). However, this study was not selected because mice and dogs were more sensitive to the old technical (71% a.i.) than rats. There are no studies in dogs or mice with the 98% a.i. technical and differences in species sensitivity (i.e rat vs dog or rat vs mouse) for long-term exposure could not be assessed.

$$\textbf{Chronic RfD} = \frac{3.0 \text{ mg/kg/day}}{100 \text{ (UF)}} = \textbf{0.03 mg/kg/day}$$

2.3 Occupational/Residential Exposure

2.3.1 Short-term (1-7 days) Incidental Oral Exposure

Study Selected: None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not Applicable

Uncertainty Factor(s): Not Applicable

Comments about Study/Endpoint/Uncertainty Factor: No appropriate endpoint was identified for this exposure scenario. Maternal effects in the developmental rabbit study were not used because decreased food consumption was not accompanied by decreased body weight and clinical signs in this study were believed to be pregnancy related, and thus not related to the population of concern (infants and children). The 90-day mouse study selected for the intermediate-term incidental oral exposure (see below), was not used because hepatic toxicity in this study is not believed to occur after 1-7 days exposure.

2.3.2 Intermediate-term (7days to several months) Incidental Oral Exposure

Study Selected: 90-day toxicity study in mice. 870.3100 (82-1a)

MRID No.: 0017602

Executive Summary: In a 3-month dietary toxicity study (MRID 00117602), Goal (72.5%) was administered to Charles River CD-1 mice (15/sex/group) at dietary concentrations of 0, 200, 800, or 3200 ppm for 13 weeks. Doses were equivalent to 0, 32.0, 134.5, or 490.5 mg/kg/day in males and 0, 44.4, 166.6, or 520.9 mg/kg/day in females. Dietary concentrations were adjusted for per cent active ingredient. Diets were adequately tested for test material concentration and homogeneity (MRID 42142316). Treatment-related mortality was limited to the high-dose group and began after 4 days of treatment. A total of 9 male and 2 female deaths during the first 2 weeks of the study were considered treatment-related. Lethargy, passiveness, ataxia, and arched backs were seen before death and in some surviving mice in the high-dose group. Yellow- or brown-stained urogenital areas and red-staining on cage bottoms were seen in all treatment groups except for low-dose females. Other clinical signs were not noted. Body weights were decreased during only the first 3 weeks in high-dose males and the first 2 weeks in high-dose females. Body weights were comparable to controls for other time periods and for other treatment groups. Food consumption was decreased in mid-dose males and mid- and high-dose males and females. Anemia was most evident in high-dose males and females but there were also decreases in hematological parameters in low- and mid-dose males and mid-dose females. Hemoglobin was decreased -10%, -14%, and -30% in low-, mid-, and high-dose males, respectively, and -3%, -9%, -25% in low-, mid-, and high-dose females, respectively in comparison to controls at termination. Associated changes in erythrocyte morphology in high-dose males and females included polychromasia, poikilocytosis, anisocytosis, nucleated erythrocytes, target cells, schistocytes, and Howell-Jolly bodies. Howell-Jolly bodies were also seen in mid-dose females. Platelets were increased approximately 100% in high-dose males and females in comparison to controls. White blood cell counts were increased in high-dose males (+153%) and females (+337%). Abnormalities in serum enzymes included elevated SGPT in low-dose females (+295%), mid-dose males (+353%) and females (+638%), and high-dose males (+1177%) and females (+1464%) in comparison to controls. Serum alkaline phosphatase was elevated in mid-dose males (+179%) and females (+109%) and to a greater extent in high-dose males (+1753%) and females (+990%) in comparison to controls. GGT was elevated in mid-dose males and females. Cholesterol was elevated in low-dose females (+55%), mid-dose males (+76%) and females (+145%), and high-dose males (+282%) and females (+483%) in comparison to controls. Glucose was decreased in high-dose males (-43%) and females (-17%) in comparison to controls. Creatinine was elevated +23% in high-dose males and +18% in high-dose females. Ketonuria occurred in urine from all female treatment groups at week 11. At week 13, urine was darker in color in a dose-related manner in both sexes. Mixed function oxidase liver enzyme activity in liver slices as determined by p-nitroanisole demethylation was determined at study termination. Activity was increased in mid-dose females and high-dose males and females. Increased liver microsomal protein was also increased in high-dose males. Absolute and relative liver weights were increased in low-dose (+26%/+22%), mid-dose (+71%/+63%), and high-dose males (+295%/+274%) and in low-dose (+10%/+10%), mid-dose (+62%/+62%), and high-dose females (+245%/+243%). At necropsy, enlarged livers were seen in 3/5 surviving high-dose males and 11/13 surviving high-dose females; many of these livers were darkened in females. Microscopic lesions in the liver included diffuse hypertrophy (all treatment groups), single-cell necrosis (low-dose females and mid- and high-dose males and females), focal necrosis (mid- and high-dose males), hemosiderosis (all treatment groups), and bile duct proliferation (high-dose males and females). Microscopic lesions of the spleen included atrophy (high-dose males) and red-pulp hyperplasia (all male treatment groups and high-dose females). Bone marrow hyperplasia was present in low-dose males and mid- and high-dose males and females. Vacuolation of the adrenal cortex was present in high-dose females. Thymic atrophy occurred in high-dose males and females. The **NOAEL** is < 200 ppm (32.0 mg/kg/day in males and 44.4 mg/kg/day in females), the lowest dose tested. The **LOAEL** is # 200 ppm (32.0 mg/kg/day in males and 44.4 mg/kg/day in females) based upon anemia, elevated liver enzymes (SGPT in females), increased liver weight, and microscopic liver lesions (single-cell necrosis in females and diffuse hypertrophy in males and females). Not all entries in HED's microfiche copy of the study report were clearly readable; this did not interfere with verifying conclusions reported here, however. Several clinical pathology analyses were not performed: blood clotting measurements, electrolytes, and SGOT. These deficiencies did not interfere with interpretation of toxicity observed in this study. This study is classified **acceptable/guideline** and **satisfies** requirements for a subchronic toxicity study in mice with oxyfluorfen.

Dose and Endpoint for Risk Assessment: **LOAEL** = 32.0 mg/kg/day based upon liver toxicity and anemia.

Comments about Study/Endpoint/Uncertainty Factor: This endpoint is appropriate for the route, duration, and population of concern. The 90-day toxicity study in rats (98% a.i.) was considered for use as an endpoint. However, this study was not selected because mice were more sensitive to the old technical (71% a.i.) than rats and no subchronic mouse study with the 98% a.i. is available.

2.3.3 Dermal Absorption

Study Selected: Dermal absorption study in rats. 870.7600, 85-2

MRID No.: 92136101

Dermal Absorption Factor: 18%

Comments about Study/Endpoint:. A dermal absorption factor was selected because the subchronic dermal toxicity study was classified unacceptable. The dermal absorption factor of 18% is the 10-hour value from the low-dose group (0.02 mg/cm^2), which had the maximal absorption of the different dose groups. The 18% value includes compound on the skin, which is considered to be potentially absorbable. The amount absorbed from the mid-dose group (0.10 mg/cm^2) at 168 hours was approximately 16%.

2.3.4 **<u>Short-Term Dermal (1-7 days) Exposure</u>**

<u>Study Selected:</u> Developmental toxicity in rabbits. Guideline #: 870.3700 (83-3b)

<u>MRID No.:</u> 44933102

<u>Executive Summary:</u> In a developmental toxicity study (MRID 44933102), oxyfluorfen (98.0% a.i.) in 1% (w/v) methylcellulose was administered to pregnant New Zealand White rabbits (15/dose) at dose levels of 0, 10, 30, or 90 mg/kg/day by gavage on gestation days (GDs) 6 through 19. Does were sacrificed on GD 29. Two premature deaths occurred in the control group; one female was sacrificed *in extremis* on GD 20 due to an ulceration on the ventral neck area and a second female aborted on GD 21. At 90 mg/kg, one female was found dead on GD 28, and two other females aborted on GD 27 or GD 29; all three females displayed reduced food consumption and fecal output from mid-gestation resulting in decreased body weight and general thin appearance prior to death. No treatment-related changes in body weight were noted at any dose level tested. At 90 mg/kg, clinical signs were observed as follows (% incidence in total animal days): little food eaten (26.4% vs 5.0% in controls); few/loose feces in undertray (28.0% vs 11.2% in controls); and thin build (6.6% vs 0% controls). Decreases (not statistically significant) were noted in food consumption during GDs 13-28 (98-38%). At necropsy, the three females that died or aborted during the study appeared thin and exhibited accentuated lobular pattern of the liver. A decrease (not statistically significant) was observed in gravid uterine weight (920%) when compared to concurrent controls. The **maternal LOAEL** is 90 mg/kg/day, based on increased mortality and abortions, clinical signs of toxicity, and decreased food consumption and gravid uterine weight. The **maternal NOAEL** is 30 mg/kg/day. There was an increase in the number of late resorptions/doe (not statistically significant, 2.5/doe vs 0.9/doe in controls) and a decrease in the number of live fetuses/doe at 90 mg/kg/day (7.1/litter vs 9.6/litter in controls). Pregnancy rates and mean fetal weights were comparable among treatment groups, as were external, visceral, and skeletal observations at necropsy. The **developmental LOAEL** is 90 mg/kg/day based on increased late resorptions and decreased number of live fetuses/doe. The **developmental NOAEL** is 30 mg/kg/day. This developmental toxicity study is classified **acceptable/non-guideline** and satisfies the guideline requirement for a developmental toxicity study in the rabbit. The study is classified non-guideline because there were 15 animals per group rather than 20.

<u>Dose and Endpoint for Risk Assessment:</u> The **maternal NOAEL** is 30 mg/kg/day. The **maternal LOAEL** is 90 mg/kg/day, based on increased mortality and abortions, clinical signs of toxicity, and decreased food consumption and gravid uterine weight.

<u>Comments about Study/Endpoint:</u>. An acceptable dermal toxicity study is not available. The developmental toxicity study was selected because the endpoints of concern

(abortions and clinical signs) are relevant for female workers. Since an oral study was selected, an 18% dermal absorption factor was selected for route-to-route extrapolation.

2.3.5 Intermediate-Term Dermal (7 Days to several months) Exposure

Study Selected: 90-day toxicity study in mice. 870.3100 (82-1a)

MRID No.: 0017602

Executive Summary: See intermediate-term incidental oral section of this document.

Dose and Endpoint for Risk Assessment: **LOAEL** = 32.0 mg/kg/day based upon liver toxicity and anemia.

Comments about Study/Endpoint: An acceptable dermal toxicity study is not available. The liver toxicity seen after 90 days was also seen after chronic exposure. Since an oral study was selected, an 18% dermal absorption factor was selected for route-to-route extrapolation.

2.3.6 Long-Term Dermal (several months to lifetime) Exposure

Study Selected: Chronic toxicity study in dogs. 870.4100 (83-1)

MRID No.: 00078767
and
Study Selected: Carcinogenicity study in mice 870.4200 (83-2a)

MRID No.: 00037939

Executive Summaries: See the chronic RfD section of this document.

Dose and Endpoint for Risk Assessment: NOAEL = 3.0 mg/kg/day based upon liver toxicity occurring in mice and dogs.

Comments about Study/Endpoint:. This study/dose/endpoint was also used for establishing the chronic RfD. Since an oral study was selected, an 18% dermal absorption factor was selected for route-to-route extrapolation.

2.3.7 Short-Term Inhalation (1-7 days) Exposure

Study Selected: Developmental toxicity in rabbits. Guideline #: 870.3700 (83-3b)

MRID No.: 44933102

Executive Summary: See short-term dermal exposure section of this document.

Dose and Endpoint for Risk Assessment: The **maternal NOAEL** is 30 mg/kg/day. The **maternal LOAEL** is 90 mg/kg/day, based on increased mortality and abortions, clinical signs of toxicity, and decreased food consumption and gravid uterine weight.

Comments about Study/Endpoint:. An acceptable inhalation toxicity study is not available. The developmental toxicity study was selected because the endpoints of concern (abortions and clinical signs) are relevant for female workers. Since an oral study was selected, for route-to-route extrapolation, inhalation exposure shall be considered equivalent to oral exposure (100%, default value).

2.3.8 Intermediate-Term (7-days to several months) Inhalation Exposure

Study Selected: 90-day toxicity study in mice. 870.3100 (82-1a)

MRID No.: 0017602

Executive Summary: See intermediate-term incidental oral section of this document.

Dose and Endpoint for Risk Assessment: **LOAEL** = 32.0 mg/kg/day based upon liver toxicity and anemia.

Comments about Study/Endpoint: An acceptable inhalation toxicity study is not available. The liver toxicity seen after 90 days was also seen after chronic exposure. Since an oral study was selected, for route-to-route extrapolation, inhalation exposure shall be considered equivalent to oral exposure (100%, default value).

2.3.9 Long-Term Inhalation (several months to lifetime) Exposure

Study Selected: Chronic toxicity study in dogs. 870.4100 (83-1)
MRID No.: 00078767
and
Study Selected: Carcinogenicity study in mice 870.4200 (83-2a)
MRID No.: 00037939

Executive Summaries: See the chronic RfD section of this document.

Dose and Endpoint for Risk Assessment: NOAEL = 3.0 mg/kg/day based upon liver toxicity occurring in mice and dogs.

Comments about Study/Endpoint:. An acceptable inhalation toxicity study is not available. This study/dose/endpoint was also used for establishing the chronic RfD. Since an oral study was selected, for route-to-route extrapolation, inhalation exposure shall be considered equivalent to oral exposure (100%, default value).

2.3.10 Margins of Exposure

For occupational exposure risk assessments, a margin-of-exposure (MOE) of 100 is adequate for short-term dermal or inhalation exposure risk assessments. A MOE of 300 is required for intermediate-term dermal or inhalation exposure risk assessments because of the use of LOAEL for these exposure scenarios. A MOE of 100 is adequate for long-term dermal or inhalation exposure risk assessments. The MOEs for residential exposure will be determined by the FQPA Safety Factor Committee.

2.4 Recommendation for Aggregate Exposure Risk Assessments

An acute aggregate assessment is not required because there was no appropriate endpoint for acute dietary exposure. A short-term aggregate exposure shall combine dermal and inhalation exposures only because there was no acute dietary endpoint. Intermediate- and long-term aggregate assessments shall combine oral, dermal, and inhalation exposures.

3 CLASSIFICATION OF CARCINOGENIC POTENTIAL

3.1 Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No.: 00083445

Executive Summary: In a chronic toxicity/carcinogenicity study (MRID 00083445, 00135072, 92136061), RH-2915 technical (Lot #: PL 75/8006 (85.7% a.i.); SW/0190-A 9-7063 (85.7% a.i.); SW 75/0174 (82.2% a.i.) was administered in the diet to groups of 50 male and 50 female Long Evans rats at concentrations of 1.0, 20.0, or 400.0 ppm for weeks 1–2; 1.4, 28.3, or 565.6 ppm for week 3–4; 2.0, 40.0, or 800.0 ppm for weeks 5–56 (800 ppm was actually 686 ppm for weeks 6-48); and 2.0, 40.0, or 1600 ppm for weeks 57–104. Based on % active ingredient, doses in males were approximately equivalent to 0, 0.10, 1.94, and 56.96 mg/kg/day, and in females were 0, 0.12, 2.43, and 72.57 mg/kg/day, in the respective dose groups. The mortality rate at study termination was 54, 48, 52, and 40% for male and 22, 40, 26, and 20% for females administered the control, low, mid, and high doses, respectively; no treatment-related effect was observed. No treatment-related clinical signs or masses were observed in either sex. Body weights of high-dose group male rats were similar to those of controls throughout the study except for a statistically significant (p<0.01) 26% decrease during week 0. No treatment-related decreases in weight gain were observed for treated male rats; male controls lost 31 and 35% more weight than mid- and high-dose rats, respectively, during the second year of treatment. Body weights for low-, mid- and high-dose group females were 9, 7, and 11% less (p<0.01 or <0.05) than control weights at most time points during the study. Body weight gain for all treated female groups was 9–12% less than that of controls for the first year of treatment and 9–10% less overall. No dose-response relationships were observed for the effects on body weights and weight gain in females suggesting that the effects were not treatment-related. No treatment-related effects were observed on hematologic or the clinical chemistry parameters evaluated in this study. Absolute and/or relative organ weights in the high-dose groups that showed statistically significant changes relative to control weights (thyroid gland in both sexes and kidney in females at 12 months and brain, pituitary, and spleen in females sacrificed at 24 months) had no microscopic correlates and are not considered toxicologically significant. Gross lesions were not observed in animals sacrificed at 12 or 24 months. Microscopic changes observed at 12 months included binucleate hepatocytes (6/10), central lobular hepatocyte hypertrophy (7/10), and enlarged hepatocyte nuclei (6/10) in high dose females compared to 0/5 for controls. Similar changes were not seen at the terminal sacrifice, despite the fact that the animals received higher doses during the last 12 months of the study. Therefore the findings at 12 months may be an adaptive effect. The changes that were statistically increased in the 24-month group were polypoid hyperplasia of the papillary epithelium in the kidney of high dose females (20/40 vs 13/45 controls, p<0.05) and cortical cysts in the kidney of mid- and high-dose males (6/25 (p<0.01) and 4/40 (p<0.05) vs 0/45 for controls). The lack of a dose-response relationship for the changes in males and the high background for the finding in females suggest that the microscopic findings were not treatment related. The **NOAEL** is $ 56.96 mg/kg/day in males and $ 72.57 mg/kg/day in females, the highest dose group. A **LOAEL** was not determined. No treatment-related neoplastic lesions were observed in either male of female rats receiving the test material under this study protocol. Dosing was not considered adequate for assessing carcinogenicity because no treatment-related effects were observed at any dose. In addition, dosages were varied during the course of the study. Animals received substantially lower doses at the beginning of the study than at the latter part of the study. This study is classified unacceptable because no treatment-related toxicity occurred in the study and because there were a number of deficiencies in this 1977 study which would not meet current guideline requirements. The study was, however, adequate to determine a NOAEL value.

<u>Discussion of Tumor Data:</u> There were no treatment-related increases in tumors in this study.

<u>Adequacy of the Dose Levels Tested:</u> No treatment-related toxicity occurred in this study at the high dose of 1600 ppm (56.96 mg/kg/day in males and 72.57 mg/kg/day in females). However, the mouse carcinogenicity study was used to determine a Q_1^* at a lower dose (33.0 mg/kg/day for males and 42.0 mg/kg/day for females, see the following section) than would occur if the rat study were repeated. A new combined chronic toxicity/carcinogenicity study in rats is **not** required.

3.2 Carcinogenicity Study in Mice

MRID No.: 00037939

Executive Summary: See chronic reference dose section of this document.

Discussion of Tumor Data: Combined hepatocellular adenomas and carcinomas were increased in 200 ppm males (8/52 vs 1/47 and 0/47 in the 2 control groups). Tumors were not increased at the lower doses. This study was used to determine the Q1* for oxyfluorfen (Health Effects Division Peer Committee memo, Kerry Dearfield, Ph.D., 9/29/89).

Adequacy of the Dose Levels Tested: The 1989 HED Peer Committee memo cited above said that dosing was inadequate because a higher dose could have been tolerated. However, dosing was sufficient to derive a Q_1* and a new carcinogenicity study was not requested from the registrant. The Peer Review memo stated: "... if the registrant feels that the liver tumors are not of concern, additional studies, such as a mouse and/or a rat oncogenicity study, at higher, more appropriate dosing, could be performed."

3.3 Classification of Carcinogenic Potential

In accordance with the 1986 guidance for carcinogenic risk assessment, the Cancer Peer Review Committee has classified oxyfluorfen as a category C, possible human carcinogen based upon combined hepatocellular adenomas/carcinomas in the mouse carcinogenicity study. The Cancer Peer Review Committee recommended a linear, low dose extrapolation for human risk assessments. The $Q_1^* = 7.32 \times 10^{-2}$ (Lori Brunsman memo, HED doc. 012879, 9/24/98).

4 MUTAGENICITY

Table 1 presents summarized findings of the acceptable genetic toxicology assays performed with formulations of oxyfluorfen containing ≥96% of the active ingredient (ai). As shown, samples of 97.1 or 99.7 % ai were negative in the mouse lymphoma assay. Single studies with Chinese hamster ovary (CHO) cells (gene mutation and chromosome aberrations) as well as bacterial DNA damage were also negative with the 99.2 or 97.1% formulations, respectively. *In vivo* studies performed with either 96% (mouse micronucleus and unscheduled DNA synthesis, UDS, in rat hepatocytes assays) or 97.1% (mouse cytogenetic assay) were negative up to or in excess of the limit dose (2000 mg/kg). Only the data from the Ames assays showed conflicting results; the findings were as follows:

Negative up to 7500 µg/plate--no compound precipitation-----------------------------99.7%
Positive in TA100 at high insoluble levels (≥1667 µg/plate +S9)-----------------------96%
Negative up to an insoluble dose (5000 µg/plate)--------------------------------------96%
Negative but currently unacceptable up to 5000 µg/plate; insoluble at
≥1667 µg/plate---99.2%

It was noted that the Ames assays performed on the 96% test product were conducted by two different contract laboratories and each study consisted of two independent trials. The summary presentation of the results from various test systems with oxyfluorfen purity levels of 96-99.7% indicate that the test material is devoid of mutagenic activity. There are, however, conflicting results for the Ames assays which were not reconciled by testing various lots or purity levels.

Table 2 presents data from the acceptable genetic toxicology studies performed with oxyfluorfen formulations of 71.4-73% ai and polar fractions of the 72.7% preparation. In agreement with the *in vivo* results for the purified samples, regardless of the percentage ai in the test material, oxyfluorfen had no adverse effect on the chromosomes of two rodent species. Similarly, the lack of activity for the 73% preparation in the *in vitro* UDS assay is consistent with the negative findings for 96% oxyfluorfen *in vivo*. The polar fraction of the test material (derived from RH-2915, lot no. 2-3985, 73% ai) was also negative for UDS *in vitro*. However, samples containing 71.4 or 72.7% ai were confirmed mutagenic for *Salmonella typhimurium* strains TA98 and TA100 either with S9 (both samples) or without S9 (72.7% ai only) at concentrations as low as 250 µg/plate +S9 (TA100). In the absence of S9 activation, mutagenicity was either not reproducible or generally confined to high levels. S9-activated lot no. 2-3985 (72.7% ai) was also mutagenic in the mammalian cell gene mutation mouse lymphoma assay. Although the response was not dose related, increased mutation frequencies were recorded at 1.97 to 40 µg/mL +S9; higher concentrations were insoluble.

A comparative analysis of the different ai percentages showed that attempts to purify the test material were partially successful as indicated by the negative response in the mouse lymphoma assay for the 99.7% formulation (see Table 1). However, despite the data showing that the bacterial mutagenic components could be isolated in a polar fraction (Table 2), as discussed earlier, there were conflicting data for the 96% ai samples in the Ames test. It has also been mentioned that both samples were from the same lot number and that the bacterial assays were independently conducted by two contract laboratories. Nevertheless, one laboratory produced confirmed negative results while the other laboratory reported confirmed evidence of a positive response in *S. typhimurium* strain TA100 at high insoluble S9-activated doses.

CONCLUSIONS: It could be concluded that the positive Ames findings in one laboratory were not confirmed in an independent reassessment of the purified test material and, thus, have no biological relevance. However, the mutagenic profile of the purified test material *(i.e,.* positive in strain TA100 at high insoluble levels, $1667 µg/plate +S9) is similar to the response induced in the same strain by separate lots containing 71.4 or 72.7% oxyfluorfen. Based on these considerations, the overall data showing a lack of mutagenicity in all test systems except the Ames assay support the use of the results as bridging data for oxyfluorfen. The data do not, however, rule out the mutagenic activity of the test article for *S. typhimurium* strain TA100. No further testing is warranted at this time. The acceptable studies performed with the $96% ai satisfy the 1991 mutagenicity guidelines.

Table 1. Genetic Toxicology Profile of Oxyfluorfen Formulations Containing $96 % Active Ingredient

Assay	Test Material			MAID No.	Result
	ID	Lot No.	Purity (%)		
Ames	RH-2915	TTF068	99.7	00098421	Neg. to HDT (7500 µg/plate); no ppt.
Mouse Lymphoma	RH-2915	0453	99.7	00098419	Neg; ppt at $62.5 µg/mL
Ames [a]	AG 510 Tech.	252/1	96	44942801	**Pos. TA 100 at high insoluble doses ($1667 µg/plate +S9)**
Ames [a]	AG 510 Tech.	252/1	96	44933104	Neg to HDT (5000 µg/plate); insoluble at this level
Mouse Micronucleus	AG 510 Tech.	P-8	96	44933105	Neg to HDT (2000 mg/kg, ip); cytotoxic to bone marrow
In vivo Rat UDS	AG 510 Tech.	P-8	96	44933106	Neg to HDT (2000 mg/kg)
Ames	Goal Herb	NA	99.2	44947206	Neg; unacceptable but upgradable
Mouse Lymphoma	Goal Tech Herb	NA	97.1	44947202	Neg; **ppt. not reported**
CHO/HGPRT	Goal Tech Purified Herb	NA	99.2	44947205	Neg; ppt at $50 µg/mL
CHO/Chromo Aberrations	Goal Tech Purified Herb	NA	99.2	44947204	Neg; ppt at $450 µg/mL
In vivo Mouse Cytogenetics	Goal Tech Purified Herb	NA	97.1	44947203	Neg to HDT (5000 mg/kg)
Bacterial DNA Damage/Repair	Goal Tech Herb	NA	97.1	44947201	Neg; ppt. at 1000 µg/plate

[a] The two Ames studies were conducted in different contract laboratories; each protocol required the performance of two independent trials.

Abbreviations:

HDT = Highest dose tested   ppt = precipitation   ip = intraperitoneal   NA = not available

Table 2. Genetic Toxicology Profile of Oxyfluorfen Formulations Containing $71.4 % Active Ingredient and Other Test Formulations

Assay	Test Material			MAID No.	Result
	ID	Lot No.	Purity (%)		
Ames	Goal Herb Tech	AMB18-42A	71.4	40992201	**Pos strains TA98 & TA100 at insoluble ($1600 µg/plate +S9) and soluble (900 µg/plate +S9) doses; weak unconfirmed response -S9**
In vivo Rat Cytogenetics	Goal Herb Tech	2-0956	71.4	41873801	Neg to HDT (5 g/kg)
In vivo Rat Cytogenetics	Goal Herb Tech	2-3985	72.5	00098418	Neg up to lethal dose (1.19 mg/kg)
Ames	RH-2915	2-3985	72.7	00098420	**Pos. strain TA1537 ($2500 µg/plate +S9; $6000 µg/mL -S9); TA98 ($500 µg/plate +S9; $1000 µg/mL -S9); TA100 ($250 µg/plate +S9; $2500 µg/mL -S9)**; no ppt reported
Mouse Lymphoma	RH-2915	2-3985	72.7	00109283	**Pos. 1.95-40 µg/mL +S9; no dose response; ppt at $62 µg/mL**
In vitro UDS Rat Hepato	RH-2915	7530	73	00098423	Neg to cytotox doses (25 µg/mL)
Ames	Polar fraction RH-2915, Lot #2-3985	WJZ 1861	NA	00098422	**Pos. (only tested TA98) ; 50-7500 µg/plate +/-S9 not dose related**; stronger response +S9
In vitro UDS Rat Hepato	Polar fraction RH-2915, Lot #2-3985	WJZ 1861	NA	00098424	Neg up to cytotox dose (25 µg/mL)

5 FQPA CONSIDERATIONS

5.1 Adequacy of the Data Base

There are developmental toxicity studies in rats and rabbits with both the current (98%) and non-registered (71%) technical materials. A reproduction study with non-registered (71%) technical material is available. Acute, subchronic, and developmental neurotoxicity studies are not available. The data base is adequate for evaluation of the data under the FQPA.

5.2 Neurotoxicity

No neurotoxicity studies are available. One rabbit had decreased motor activity at 90 mg/kg/day in developmental toxicity study(MRID 00094052) prior to death. Clinical signs at 848 mg/kg/day in a developmental rat study included hunched posture, ataxia, lethargy, pale extremities, alopecia, and mucoid feces; 15 rats in this group died. These effects were considered agonal and not indicative of neurotoxicity.

5.3 Developmental Toxicity:

Executive summaries for developmental toxicity studies follow. There are 2 developmental toxicity studies in rats, one with 71.4% technical oxyfluorfen, and 1 with 98.0% technical oxyfluorfen. There are 2 developmental toxicity studies in rabbits, 1 with a 26.9% WP formulation manufactured from 71% technical, and another developmental toxicity study in rabbits with 98.0% technical oxyfluorfen.

1981 Developmental toxicity study in rabbits with wettable powder formulation from 71% technical:

CITATION: Hoberman, A.M., M.S. Christian, and G.D. Christian (1981) Goal herbicide - teratogenicity study in rabbits. Argus Research Laboratories, Inc.. Argus Project 018-006, November 26, 1981. MRID 00094052. Unpublished.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 00094052), 19 presumed pregnant New Zealand White rabbits per group were administered oxyfluorfen (26.9% ai; Lot No. CDP 0482-1) by gavage at dose levels of 0 (negative control), 0 (vehicle control), 10, 30, or 90 mg/kg/day, on gestation days (GD) 6-18, inclusive. Doses were adjusted for per cent active ingredient. The vehicle control consisted of all ingredients of the 25 WP formulation without the active ingredient administered at the equivalent of a 90 mg/kg/day dose of 25 WP. Five premature deaths and 4 abortions occurred in the 90 mg/kg/day treatment group. Treatment related clinical signs of toxicity consisted of anorexia and red exudate in the cage pan at 30 and 90 mg/kg/day and hematuria and decreased motor activity at 90 mg/kg/day of oxyfluorfen. Ulceration, erosions, and/or petechial hemorrhages were observed at necropsy in the stomach mucosa of 3 high-dose does which died. Body weight gain was decreased during GD 13-18 at 30 mg/kg/day and throughout the dosing at 90 mg/kg/day; terminal body weights were not significantly affected at any dose level.

The maternal toxicity LOAEL is 30 mg/kg/day based on decreased body weight gain during treatment and clinical signs of toxicity. The maternal toxicity NOAEL is 10 mg/kg/day.

Decreased litter size and an increase in early resorptions occurred at 90 mg/kg/day. The small number of litters (5/11 pregnant does) evaluated precluded adequate statistical evaluation of cesarean section data. There were no treatment-related external, visceral, or skeletal malformations or variations observed at any treatment level. There was no evidence for delayed fetal growth at any treatment level compared to controls.

The developmental toxicity LOAEL is 90 mg/kg/day based on decreased litter size and increased early resorptions. The corresponding fetal developmental toxicity NOAEL is 30 mg/kg/day. This study is classified **acceptable/non-guideline** and satisfies the guideline requirements for a developmental toxicity study in rabbits.

<u>1997 Developmental toxicity study in rabbits with 98% technical:</u>

<u>CITATION</u>: Burns, L.M. (1997). Oxyfluorfen Technical: Study of Embryo-Fetal Toxicity in the Rabbit by Oral Gavage Administration. Huntingdon Life Sciences Ltd., Suffolk, England. Laboratory Report # 96/AGN074/1147, February 5, 1997. MRID 44933102. Unpublished.

<u>EXECUTIVE SUMMARY:</u> In a developmental toxicity study (MRID 44933102), oxyfluorfen (98.0% a.i.) in 1% (w/v) methylcellulose was administered to pregnant New Zealand White rabbits (15/dose) at dose levels of 0, 10, 30, or 90 mg/kg/day by gavage on gestation days (GDs) 6 through 19. Does were sacrificed on GD 29. Two premature deaths occurred in the control group; one female was sacrificed *in extremis* on GD 20 due to an ulceration on the ventral neck area and a second female aborted on GD 21. At 90 mg/kg, one female was found dead on GD 28, and two other females aborted on GD 27 or GD 29; all three females displayed reduced food consumption and fecal output from mid-gestation resulting in decreased body weight and general thin appearance prior to death. No treatment-related changes in body weight were noted at any dose level tested. At 90 mg/kg, clinical signs were observed as follows (% incidence in total animal days): little food eaten (26.4% vs 5.0% in controls); few/loose feces in undertray (28.0% vs 11.2% in controls); and thin build (6.6% vs 0% controls). Decreases (not statistically significant) were noted in food consumption during GDs 13-28 (98-38%). At necropsy, the three females that died or aborted during the study appeared thin and exhibited accentuated lobular pattern of the liver. A decrease (not statistically significant) was observed in gravid uterine weight (920%) when compared to concurrent controls. The **maternal LOAEL** is 90 mg/kg/day, based on increased mortality and abortions, clinical signs of toxicity, and decreased food consumption and gravid uterine weight. The **maternal NOAEL** is 30 mg/kg/day. There was an increase in the number of late resorptions/doe (not statistically significant, 2.5/doe vs 0.9/doe in controls) and a decrease in the number of live fetuses/doe at 90 mg/kg/day (7.1/litter vs 9.6/litter in controls). Pregnancy rates and mean fetal weights were comparable among treatment groups, as were external, visceral, and skeletal observations at necropsy. The **developmental LOAEL** is 90 mg/kg/day based on increased late resorptions and decreased number of live fetuses/doe. The **developmental NOAEL** is 30 mg/kg/day

This developmental toxicity study is classified **acceptable/non-guideline** and satisfies the guideline requirement for a developmental toxicity study in the rabbit.

1991 Developmental toxicity study in rats with 71.4% technical oxyfluorfen:

CITATION: Solomon, H.M. and Romanello, A.S. (1991) Goal: oral (gavage) developmental toxicity study in rats. Rohm and Haas Company, Spring House, PA. Study Number: 90R-008. Unpublished. 2/15/91. MRID 41806501. Unpublished.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 41806501), oxyfluorfen (71.4%), was administered by gavage to pregnant Crl:CD BR rats from gestation days 6-15. There were 27 rats/group. Doses were 0, 18, 183, or 848 mg/kg/day (adjusted for analytical results). Maternal mortality occurred in the high-dose group: 15 rats died or were sacrificed. Maternal clinical signs in the mid-dose group included red vaginal discharge, soft feces, scant feces. Clinical signs in the high-dose group also included hunched posture, ataxia, lethargy, pale extremities, alopecia, and mucoid feces. Overall body weights and weight gains for low- and mid-dose groups were generally comparable to controls, and were not compared for the high-dose group due to the high mortality in this group. Altered clinical pathology parameters in the high-dose group included elevated alkaline phosphatase and SGOT, and increases in leukocyte count, mean cell volume, and platelets. Mean corpora lutea, implantations, and pregnancy rates were similar in all treatment groups. There were no live pups in the high-dose group due to a 100% early resorption incidence. Mean early resorptions were also increased in the mid-dose group (0.9, 0.5, and 2.7 in control, low-, and mid-dose groups respectively) resulting in decreased live fetuses and increased postimplantation loss. Mean fetal weight was decreased in the mid-dose group (84% of control value) and were comparable to controls in the low-dose group. There were 4 litters in the mid-dose group with vessel variations compared to 1 litter in the control group (Table 1). There were 12 litters in the mid-dose group with skeletal malformations which included bent scapula, fused sternebrae, and bent bones in hindlimbs and forelimbs compared to 0 litters in the control group with skeletal malformations. The **NOAEL for maternal toxicity** is 18 mg/kg/day; the **maternal LOAEL** is 183 mg/kg/day based on clinical signs. The **NOAEL for developmental toxicity** is 18 mg/kg/day. The **LOAEL for developmental toxicity** is 183 mg/kg/day based on increased early resorptions, decreased fetal weight, and increased incidence of fetal visceral and skeletal variations and malformations.

1997 Developmental toxicity study in rats with 98.0% technical:

CITATION: Burns, L.M. (1997). Oxyfluorfen Tech: Study of Embryo-Fetal Toxicity in the CD Rat by Oral Gavage Administration. Huntingdon Life Sciences Ltd., Suffolk, England. Laboratory Report # 96//AGN075/1054, January 30, 1997. MRID 44933103. Unpublished.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44933103), oxyfluorfen (98.0% a.i.) in 1% (w/v) methylcellulose was administered to pregnant CD Sprague-Dawley rats (22/dose) at dose levels of 0, 375, 750, or 1000 mg/kg/day (limit dose) by gavage on gestation days (GDs) 6 through 15. Dams were sacrificed on GD 20.

No premature deaths or clinical signs of toxicity were observed at any dose level tested. When compared to concurrent controls, no treatment-related changes in body weight, food consumption, gross pathology, or reproductive parameters were noted at any dose level tested. The **maternal LOAEL** was not observed. The maternal **NOAEL** is $ 1000 mg/kg/day (limit dose). No developmental toxicity was noted at any dose level tested. The **developmental LOAEL** was not observed. The **developmental NOAEL** is $ 1000 mg/kg/day. This developmental toxicity study is classified **acceptable/guideline** and satisfies the guideline requirement for a developmental toxicity study in the rat.

5.4 **<u>Reproductive Toxicity:</u>** There is 1 reproductive toxicity study with oxyfluorfen. This study used 71.4% technical oxyfluorfen.

<u>Two-generation reproductive toxicity study with 71.4% technical</u>

<u>CITATION</u>: Solomon, H.M., W.R. Brown, R.E. Swenson, and T.L. Thomas (1991) Goal® Technical Herbicide: Two generation reproduction study in rats. Rohm and Haas Company, Toxicology Department, Spring House, PA 19477. Report No. 90P-007. August 26, 1991. MRID 42014901. Unpublished.

<u>EXECUTIVE SUMMARY</u>: Goal Herbicide (71.4% a.i.; Lot No.: 2-0956) was administered to groups of 25 male and 25 female Crl:CD®BR rats in the diet at concentrations of 0, 100, 400, or 1600 ppm of active ingredient for two generations (MRID 42014901). One litter was produced in each generation. Premating doses for the adult F_0 males were 0, 7.8, 30.9, and 120.0 mg/kg/day and for the F_0 females were 0, 8.5, 32.8, and 131.2 mg/kg/day, respectively. Premating doses for the adult F_1 males were 0, 8.9, 36.4, and 146.3 mg/kg/day and for the F_1 females were 0, 8.9, 35.7, and 151.3 mg/kg/day, respectively. F_1 pups chosen to produce the F_2 litters were weaned onto the same diets as their parents. Animals were given test or control diet for 10 (F_0) or 14 (F_1) weeks then mated within the same dose group. One high-dose F_1 male was sacrificed moribund during week 9 of treatment; treatment-related chronic pyelonephritis secondary to pelvic mineralization was described at necropsy; this death was attributed to treatment. No treatment-related clinical signs of toxicity were observed in parental animals of either generation. Several intercurrent deaths of F_0 females and F_1 males and females were considered incidental to treatment. Mean body weights, body weight gains, and food consumption by the low- and mid-dose males and females of both generations were comparable to their respective controls. Body weights of the high-dose F_0 males were slightly (n.s.) lower than the controls throughout premating with overall body weight gains 92% of the control level. Absolute body weights of the high-dose F_0 females were significantly (p # 0.05) less than the controls during weeks 4-7, with overall body weight gain 88% of controls. Food consumption by the high-dose F_0 males was significantly (89-92% of control; p # 0.05) less than the controls during weeks 0, 2, and 4-8 of the premating interval. Food consumption by the high-dose F_0 females was 85-94% of the control levels during the premating period with statistical significance (p # 0.05) reached during weeks 0-6 and 8. High-dose F_1 males and females had significantly (p # 0.05) lower body weights than the controls throughout the premating interval (84-89% and 79-93%, respectively of the controls). Overall body weight gains were 89% and 97%, respectively, of control levels. Food consumption was significantly (p # 0.05) less than the controls by the high-dose F_1 males during treatment weeks 0-9 and 12 and by high-dose F_1 females during weeks 0-3, 5, and 8.

High-dose F_0 dams had significantly (p # 0.05) lower body weights than the controls on GD 21 and on lactation day 14. Body weights of the high-dose F_1 dams were significantly (p # 0.05) less than the controls throughout gestation and on lactation days 0, 7, and 14. Body weights of the high-dose F_1 pups were significantly (78-89% of controls; p # 0.05) less than the controls throughout lactation. High-dose F_2 pups had significantly (82-89%; p # 0.05) lower body weights than the controls on lactation days 0, 14, and 21. Body weight gains by the high-dose pups of both generations were 81-85% of the control level for lactation days 0-14 and were 73-77% of the control level for lactation days 14-21. Because the most pronounced effect on pup body weight gain was after they started to eat the test diets, the lower pup body weights are considered a systemic effect and not a lactational effect. No treatment-related findings were observed at necropsy of the F_0 or F_1 females. Gritty material was observed in the renal pelvis of 2/25 high-dose F_0 males and in 1/25 and 5/25 mid- and high-dose F_1 males, respectively. This was not observed in any control or low-dose males. Dose-related increases in the incidence rates of liver and kidney lesions were observed in males and females of both generations. Hepatocellular hypertrophy was observed in 1/25, 1/25, 1/25, and 12/25 (p # 0.01) F_0 males; in 1/25, 0/25, 0/25, 14/25 (p # 0.01) F_0 females; in 2/25, 2/25, 1/25, 17/25 (p # 0.01) F_1 males; and in 0/25, 0/25, 0/25, 8/25 (p # 0.01) F_1 females in the 0, 100, 400, and 1600 ppm groups, respectively. The incidence rates of mineralization of the renal pelvis were 0/25, 1/25, 3/25, 7/25 (p # 0.01) in F_0 males; 4/25, 2/25, 3/25, 7/25 in F_0 females; 1/25, 1/25, 5/25, 11/25 (p # 0.01) in F_1 males; and 3/25, 2/25, 8/25, 13/25 (p # 0.01) in F_1 females, respectively. In the kidney of high-dose F_1 animals, there were increased incidences of dilatation of the collecting ducts (0/25, 0/25, 2/25, 11/25 [p # 0.01] males and 1/25, 0/25, 0/25, 9/25 [p # 0.01] females) and hyperplasia of the pelvic/papillary epithelium (4/25, 5/25, 6/25, 11/25 [p # 0.05] males and 1/25, 3/25, 2/25, 8/25 [p # 0.05] females). The **LOAEL for parental toxicity** is 1600 ppm (males: 120.0 mg/kg/day; females: 131.2 mg/kg/day) based on mortality, body weight decrements, and microscopic kidney and liver lesions. The **NOAEL for parental toxicity** is 400 ppm (males: 30.9 mg/kg/day; females: 32.8 mg/kg/day). No treatment-related effects were noted on fertility or mating indices of either generation. No dose- or treatment-related effects were observed in either generation for number of litters, per cent male pups, or pup survival indices. No clinical signs of toxicity were seen in any pups from either generation. On lactation day 0 the high-dose group of both generations had significantly (p # 0.05) fewer live pups/litter and lower mean pup body weights as compared to controls. The **LOAEL for reproductive toxicity** is 1600 ppm (131.2 mg/kg/day) based on fewer live pups/litter and body weight decrements. The **reproductive toxicity NOAEL** is 400 ppm (32.8 mg/kg/day). This study is classified **acceptable/guideline** and satisfies the guideline requirement for a reproduction study (83-4) in rats.

5.5 Additional Information from Literature Sources:

A literature search on Medline and Toxline was conducted. No information was found that would affect this toxicological evaluation.

5.6 Determination of Susceptibility

In the developmental toxicity study in rats with 98% a.i., no developmental toxicity was seen at the limit dose. In the developmental toxicity study in rabbits with 98% a.i., there was no quantitative or qualitative evidence of susceptibility. Developmental toxicity, characterized as decreases in live fetuses per doe occurred at the same dose that caused maternal toxicity, including increased abortions, clinical signs, and decreased food consumption. Also, the decrease in live fetuses occurred primarily in one litter and were not statistically significant. In the two generation reproduction study in rats with 71% a.i., offspring toxicity was manifested as decreased live pups per litter and decreased pup body weight in the presence of maternal toxicity (mortality in one doe, decreased body weight gain, and liver and kidney lesions) at the same dose. The HIARC determined that any uncertainty with respect to the fetal deaths observed in this study were allayed since the pup deaths seen at Day 0, (i.e., prenatal death) were not seen at a much higher dose (1000 mg/kg/day) in the prenatal developmental toxicity study in rats conducted with the 98% a.i.

5.7 Recommendation for a Developmental Neurotoxicity Study

It is recommended that a developmental neurotoxicity study **not** be required.

5.7.1 Evidence that suggest requiring a Developmental Neurotoxicity study:

No neurotoxicity studies are available. Signs suggestive of neurotoxicity occurred in developmental studies. One rabbit had decreased motor activity at 90 mg/kg/day in developmental toxicity study(MRID 00094052) prior to death. Clinical signs at 848 mg/kg/day in a developmental rat study included hunched posture, ataxia, lethargy, pale extremities, alopecia, and mucoid feces; 15 rats in this group died. These signs are attributed to agonal death.

5.7.2 Evidence that **does not** support the need for a Developmental Neurotoxicity study

The above mentioned signs suggestive of neurotoxicity occurred at lethal doses and were considered agonal. There were no gross or microscopic neurotoxic lesions of treatment-related damage to the nervous system. No increase in susceptibility of fetuses or offspring occurred in developmental or reproductive studies.

6 HAZARD CHARACTERIZATION:

Oxyfluorfen is of low acute toxicity. Oxyfluorfen is in toxicity category IV for acute oral and inhalation toxicity and is category III for acute dermal toxicity. Oxyfluorfen is a slight eye and dermal irritant and is not a dermal sensitizer.

Toxicity at lower doses was generally not severe. Although oxyfluorfen inhibits heme synthesis, the observed anemia was generally mild. A microcytic anemia with a decreased hematocrit, small erythrocytes, and normal RBC count was described in the 1997 subchronic rat study. In other words, the red blood cell count was normal in this study, but the red blood cell mass was decreased because of the small size of the red blood cells, presumably because of inhibition of the protoporphyrinogen oxidase enzyme. The anemia was generally mild in other studies, with varying hematologic abnormalities described in the different studies.

Mild liver toxicity also occurred. Liver weights were increased and were accompanied in several studies by slightly elevated serum alkaline phosphatase enzyme, which can be elevated by increased pressure in biliary canals in the liver, as well as by other causes in other locations in the body. Other liver enzymes also had slight elevations in the various studies. There were typically few histopathological lesions seen in the liver, although hepatocyte necrosis was occasionally noted in the different studies.

Renal toxicity was most severe in the 2-generation reproduction study in rats, in which pelvic mineralization occurred. Other studies had indications of renal toxicity: increases in organ weight and occasional histopathological observations.

Other toxicological changes included weight loss, clinical signs, lacrimation, increased urine volume, and mortality.

Oxyfluorfen is classified as a category C, possible human carcinogen based upon combined hepatocellular adenomas/carcinomas in the mouse carcinogenicity study. The Cancer Peer Review Committee recommended a linear, low dose extrapolation for human risk assessments, with a Q_1^* of 7.32×10^{-2}.

There is no evidence of increased sensitivity of fetuses or offspring due to pre- or postnatal exposure to oxyfluorfen.

Oxyfluorfen and other herbicidal inhibitors of protoporphyrinogen oxidase are being evaluated by EFED and ORD for possible phototoxicity based on reports of porphyrin accumulation in test animals. Since the biosynthesis of heme is inhibited by oxyfluorfen, there is the possibility that porphyrin precursors of heme could accumulate in the skin and be activated by light and cause toxicity. There have so far been no indications that oxyfluorfen does cause phototoxicity.

7 DATA GAPS:

The HIARC recommends that a 21-day dermal study in rats and a 28-day inhalation study in rats with 98% a.i. be conducted.

8 ACUTE TOXICITY

Acute Toxicity of Oxyfluorfen

Guideline No.	Study Type	MRID	Test Material	Registrant	Results	Toxicity Category
81-1	Acute Oral	44712010	96%	Agan	LD_{50} > 5000 mg/kg	IV
		44828903	97.1%	Rohm & Haas	LD_{50} > 5000 mg/kg	IV
81-2	Acute Dermal	44712011	96%	Agan	LD_{50} > 2000 mg/kg	III
		44828904	97.1%	Rohm & Haas	LD_{50} > 5000 mg/kg	IV
81-3	Acute Inhalation	44712012	96%	Agan	LC_{50} > 3.71 mg/L	IV
		---	---	---	---	---
81-4	Primary Eye Irritation	44712013	96%	Agan	slight irritant	IV
		44828906	96%	Rohm & Haas	negative	IV
81-5	Primary Skin Irritation	44712014	96%	Agan	slight irritant	IV
		44828905	96%	Rohm & Haas	negative	IV
81-6	Dermal Sensitization	44712015	96%	Agan	Negative	---
		44814901	23%	Rohm & Haas	Negative	
81-8	Acute Neurotox	---	---	---	---	NA

9 SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	An appropriate endpoint attributed to a single dose was not available. Therefore, an acute RfD was not established.		
Chronic Dietary	NOAEL = 3.0 UF = 100	Liver toxicity occurring in dogs and mice.	Chronic dog study and mouse carcinogenicity
		Chronic RfD = 0.03 mg/kg/day	
Cancer	$Q_1^* = 7.32 \times 10^{-2}$	Combined hepatocellular adenomas and carcinomas.	Mouse carcinogenicity study
Incidental Oral, Short-Term	An appropriate endpoint attributed to short-term, incidental oral exposure was not available.		
Incidental Oral, Intermediate-Term	LOAEL = 32	Liver toxicity and anemia.	90-day mouse
Dermal, Short-Term[a]	NOAEL= 30	Abortions and clinical signs.	Developmental rabbit study (1998)
Dermal, Intermediate-Term[a]	LOAEL = 32	Liver toxicity and anemia.	90-day mouse
Dermal, Long-Term[a]	NOAEL = 3.0	Liver toxicity occurring in dogs and mice.	Chronic dog study and mouse carcinogenicity
Inhalation, Short-Term[b]	NOAEL = 30	Abortions and clinical signs.	Developmental rabbit study (1998)
Inhalation, Intermediate-Term[b]	LOAEL = 32	Liver toxicity and anemia.	90-day mouse
Inhalation, Long-Term[b]	NOAEL = 3.0	Liver toxicity occurring in dogs and mice.	Chronic dog study and mouse carcinogenicity

a An oral endpoint was used for dermal exposure: dermal absorption factor of 18% of oral exposure shall be used.
b An oral endpoint was used for inhalation exposure: inhalation exposure assumed equivalent to oral exposure.